

Endothelial Dysfunction and Diabetes

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Atherosclerosis is the leading cause of death in patients with diabetes. Accelerated atherosclerosis is also the major cause of morbidity in Diabetes and is the underlying cause of Macroangiopathy that includes Coronary Artery Disease, Stroke and Peripheral Vascular Disease. Endothelial dysfunction is believed to be the earliest functional abnormality in the blood vessels that is seen in Diabetes and serves as a very important surrogate marker for future atherosclerosis in them.

The healthy endothelium maintains vascular integrity through the release of several paracrine factors most important of which is nitric oxide. In response to atherosclerotic risk factors including Diabetes, the endothelium becomes dysfunctional. This sets of a cascade of events which ultimately leads to acceleration of atherosclerosis. Endothelium-dependant vasodilator responses can be assessed in human coronary arteries and in the peripheral circulation. In the brachial artery this is done by flow mediated dilatation (FMD).^{1,2}

Diabetes is a vascular disease and endothelial dysfunction is usually seen in diabetic patients.^{1,2,3} Decreased FMD in diabetic patients compared to non diabetic subjects has been demonstrated in south Indians.³ Several lines of evidence support the concept that endothelial dysfunction plays an important role in diabetic atherosclerotic disease. Experimental *in vitro* and *in vivo* studies show that endothelial cells exposed to a diabetic environment have a subnormal generation of NO. Insulin receptors have been demonstrated in vascular endothelium and recent evidence suggests that insulin has a vasodilatory role. Insulin resistance results in activation of PKC in vascular tissues that leads to endothelial dysfunction and vascular damage. Human studies also clearly show an association between several markers of endothelial dysfunction such as impaired endothelium dependent vasodilatation, increased levels of PAI-1, t-PA, vWF, and the soluble adhesion molecules such as E-Selectin, VCAM-1 and ICAM-1 and atherosclerosis and microvascular disease in diabetic subjects.¹ An earlier study from our centre found significantly higher levels of lipid peroxidation, and a greater endothelial dysfunction as indicated by enhanced expression of sVCAM-1 and reduced activity of NO pathway in Asian Indian patients with diabetic macroangiopathy compared to those without macroangiopathy and healthy controls thereby suggesting that both these pathways have a key role in the pathogenesis of macrovascular complications in T2DM.⁴

Several studies have reported significant endothelial dysfunction in patients with diabetes (Type 2 and Type 1) as well as in patients with insulin resistance, prediabetes and metabolic syndrome. Vasodilatory responses to acetylcholine and high plasma levels of endothelin -1 have also been demonstrated in subjects with impaired Glucose Tolerance (IGT) and in healthy Normal Glucose Tolerant (NGT) subjects who were first degree relatives of T2DM patients. This suggests that endothelial

dysfunction is a very early abnormality in the natural history of type 2 diabetes and is seen even in NGT subjects with a high risk of developing type 2 diabetes.^{1,2} Prediabetic subjects as compared to NGT subjects responded to oral fat challenge with a greater endothelial dysfunction and even more if they had familial predisposition to diabetes.⁵

The pathogenesis of endothelial dysfunction in type 2 diabetes is complex and involves many mechanisms. Visceral obesity, Insulin resistance, hypertension, post prandial hyperlipidemia particularly post prandial hypertriglyceridaemia, fasting and post prandial hyperglycemia result in an increased oxidative stress. Vascular endothelium is very susceptible to oxidative stress damage and this enhanced oxidative stress seen in diabetic individuals in turn causes endothelial dysfunction. In early stages, insulin resistance and free fatty acids act directly on e-NOS activity and mitochondrial function. This leads to oxidative stress and increase generation of superoxide radicals. Oxidative stress activates several pathways – PKC, glycation of cellular DNA and other macromolecules, polyol, hexosamine and nuclear factor KappaB pathways - all of which contribute to worsening of endothelial dysfunction in diabetes.¹ Our group has found significant postprandial hypertriglyceridaemia in patients with T2DM both in newly detected⁶ as well as in long standing known diabetes.⁷ Significant post prandial endothelial dysfunction was detected in diabetic patients particularly with macroangiopathy following an oral fat meal challenge which was associated with significant postprandial oxidative stress.⁸ We also showed that post prandial hypertriglyceridaemia is a major determinant of post prandial oxidative stress in T2DM which may lead to endothelial dysfunction and macrovascular disease.⁸

Thus, endothelial dysfunction is an early abnormality in diabetes and may play a key role in the micro and macrovascular disease associated with diabetes. Whether endothelial dysfunction causes some of the abnormalities of the metabolic syndrome and whether it can increase the risk of diabetes is unclear and merits further investigation. In a long term study on subjects with endothelial dysfunction it was shown that the risk of developing diabetes increased 6 fold.⁹

Several interventions have been shown to ameliorate endothelial dysfunction in diabetic patients. These include exercise and weight loss, lipid lowering, ACE-inhibition, antioxidant strategies, PPAR- γ agonists, reducing homocysteine levels, aspirin, reducing hyperglycaemia and more recently nitric oxide co-factors such as tetrahydrobiopterin and modulation of insulin resistance.

Improvements in endothelial dysfunction in diabetic patients has been documented with fibrates, statins, ACE inhibitors, Metformin, Niacin – ER and fish oils through large clinical endpoint trials. Other studies showing benefit but not through clinical endpoint trials include those with certain antioxidants like Vitamin E and vitamin C, L-arginine, PKC-inhibitors, PPAR- α and γ -agonists and PDE-5 inhibitors.^{1,2,10} Other agents that have improved endothelial function in T2 DM patients

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include Coenzyme Q 10, folic acid, vitamin D in those with low levels, Alpha lipoic acid, Walnuts and Sildenafil and tadalafil in men and estrogen therapy in women.¹⁰

Glycemic control per se has not been shown to affect endothelial dysfunction. Ripaglinide but not glibenclamide increased brachial artery FMD. Alpha Glucosidase inhibitor acarbose attenuated post prandial worsening of endothelial dysfunction in T2DM patients. Metformin shows mixed results on endothelial dysfunction which includes studies which had positive effects and others which had negative effects. Recombinant GLP-1 improved brachial artery FMD in some studies while others have shown no effect.¹⁰ Insulin sensitizers, pioglitazone and rosiglitazone showed increased brachial artery FMD in doubled blind placebo control trials in T2DM patients. Pioglitazone improved FMD in metformin treated T2DM patients compared with Glimeperide for similar glycemic control.¹⁰

Results of statins on endothelial dysfunction in T2DM have been inconsistent and contradictory even as several studies document their positive impact overall. Some studies have shown no effects while a few other RCTs have shown a beneficial effect on brachial artery FMD in T2DM subjects. The effect of fibrates on endothelial dysfunction in T2DM are far more consistent. Three double blind placebo controlled RCTs have shown improvement in brachial artery FMD. Studies with fibrates which reduce fasting as well as post prandial triglycerides significantly have improved fasting and post prandial endothelial function significantly in diabetic patients. Combination treatments with statins and ACE-inhibitors and statins plus fibrates have also shown additional benefit on endothelial dysfunction but no clinical outcome data for these are available. Evidence for an improvement in cardiovascular events in T2DM is still lacking with a combination of statin and fibrate even after the results of ACCORD trial recently published.^{1,2,10}

In the current issue of JAPI, Chugh et al evaluated the effect of glycaemia on FMD endothelial function in type 2 diabetic patients and have reported significant improvements in endothelial function after 12 weeks of treatment during which there was a concomitant significant improvement in glycaemic control in them. Regardless of whether these patients started with a low or very low FMD in those with fair or poor glycaemic control, the FMD values reached close to those observed in the control group once excellent glycaemic control was achieved in them. These results point to a significant reversible component of endothelial dysfunction that is amenable to good glycaemic

control at least in those diabetic subjects who did not already have evidence of clinical vascular disease such as hypertension, or other macroangiopathy. Earlier studies have not reported effects of glycaemic control in improving endothelial function in diabetes and if confirmed in a larger subset of diabetic patients the results of the present study would provide all physicians yet another reason to strive for achieving strict glycaemic control in diabetic patients.

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